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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,881	09/11/2003	Harlan W. Waksal	11245/46403	8515

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,881	WAKSAL ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,24 and 30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,24 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed 8/9/2004 is acknowledged. Claims 4-23 and 25-29 were canceled.

Claims 1-3, 24 and 30-39 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

2. Claims 1-3, 24 and 30-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the phrase "biological molecule inhibitor". The scope of claims 1 and 30 cannot be determined because the specification provides an open ended definition of "biological molecule inhibitor". Part of the problem is that one possible interpretation of "biological molecule inhibitor" is that it is any molecule that is not a "small molecule". However, the definition of "small molecule" provided on page 16 of the specification includes within its scope molecules that have molecular weights that are less than 500, which is a description that would fit a molecule that could be included within the scope of "biological molecule inhibitor", because "biological molecule inhibitor" includes within its definition, a peptide that is a CDR.

Claim 2 is indefinite because the phrase "the hypervariable region thereof" lacks antecedent basis. Antibody molecules contain six hypervariable regions (also referred to as

CDRs). This rejection would be overcome by amending the claim to recite "a hypervariable region thereof".

3. Claims 1 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that broad genus of "non-radiolabeled biological molecule inhibitor" of EGFR/Her-1 is not adequately described by the specification.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

Claim 1 is drawn to a method to inhibit the growth of a tumor that overexpresses epidermal growth factor receptor (EGFR/HER-1) in a human patient, which comprises treating said human patient with an effective amount of a combination of radiation and a non-radiolabeled biological molecule inhibitor of said EGFR/HER-1. As noted above, the specification fails to define the scope of the term "biological molecule inhibitor" of EGFR/HER-1. Additionally, the specification contemplates that a biological molecule inhibitor may include proteins, peptides or nucleic acids that inhibit the growth of cells that overexpress a growth

factor receptor tyrosine kinase (see page 10). Therefore, the undefined scope of "biological molecule inhibitor" of EGFR/HER-1 appears to include any protein or peptide or nucleic acid that inhibits EGFR/HER-1. Thus, the scope of the genus of inhibitors to be used in the claimed methods is extremely large and varied. Included in the description of "biological molecule inhibitors" are monoclonal antibodies and functional equivalents that may be molecules that comprise a CDR. Such a disclosure does not provide representative examples of structures that are encompassed by the genus of "biological molecule inhibitor" of EGFR/HER-1. For a claim drawn to a genus, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus (see Official Gazette 1241 OG 174, January 30, 2001).

In the instant case, the skilled artisan cannot envision the detailed chemical structure of the encompassed "biological molecule inhibitor" used in the method claims and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of manufacturing or testing the claimed process. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See

Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Greene (U.S. 6,417,168; issued Jul. 9, 2002; effective filing date Mar. 4, 1998).

Claims 1 and 30 are broadly drawn to methods of inhibiting the growth of a tumor that overexpresses epidermal growth factor receptor (EGFR)/Her-1 in a human patient, comprising treating said patient with an effective amount of a combination of radiation and a non-radiolabeled biological molecule inhibitor of said EGFR/HER-1. The tumor may be a tumor of the breast, lung, colon, kidney, bladder, head and neck, ovary, prostate, or brain. Claim 1 fails to contain any structural limitation on the "biological molecule inhibitor" of EGFR/HER-1.

Greene teaches and claims a method of treating a p185-mediated tumor comprising administering, in combination with radiation, a peptide that inhibits the formation of erbB protein dimers, where the dimers may p185/EGFR heterodimers (see claims 1 and 14). One of the activities of EGFR is to form heterodimers with p185(Her-2). Greene teaches that tumors

that may be treated are glial brain tumors and prostate cancers (see column 20, lines 4-18). Thus, Greene teaches a method comprising the administration of a biological molecule inhibitor of EGFR/HER-1 in combination with radiation.

5. Claims 1 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Arnold (U.S. 5,736,534; issued April 7, 1998; effective filing date July, 29, 1996; cited in the IDS).

Claims 1 and 30 are broadly drawn to methods of inhibiting the growth of a tumor that overexpresses epidermal growth factor receptor (EGFR)/Her-1 in a human patient, comprising treating said patient with an effective amount of a combination of radiation and a non-radiolabeled biological molecule inhibitor of said EGFR/HER-1. The tumor may be a tumor of the breast, lung, colon, kidney, bladder, head and neck, ovary, prostate, or brain. Claim 1 fails to contain any structural limitation on the "biological molecule inhibitor" of EGFR/HER-1.

Arnold teaches methods of treatment of cancers such as renal, linver, kidney, bladder, breast, gastrice, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, and various head and neck tumors (see col. 20, lines 24) comprising administering quinzolines of Formula I (see col. 2, lines 15-20) in combination with radiation (see column 20, lines 31-37). Thus, Arnold teaches methods that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-3, 24, and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saleh (Saleh, M. et al., Proceedings of the American association for Cancer Research, 37: 612, Abstract #4197, 1996, March; cited in the IDS) in view Goldstein (Goldstein, N.I. et al, Clinical Cancer Research, 1: 1311-1318, 1995).

The claims are drawn to methods for inhibition of growth of a tumor that overexpresses EGFR/HER-1, comprising treating a human patient with a tumor that overexpresses EGFR/HER-

1 with a combination of radiation and a non-radiolabeled monoclonal antibody. The monoclonal antibody inhibits EGFR/HER-1 phosphorylation.

Saleh teaches treating mice bearing xenograft tumors (A431 human epidermoid carcinoma) with a combination of radiation and the anti-EGFR monoclonal antibody C225. Saleh teaches that the combination resulted in better tumor control. Saleh fails to teach treatment of human patients and fails to teach chimerized or humanized anti-EGFR monoclonal antibodies. Goldstein teaches a chimerized version of C225 (cC225) antibody and teaches that it is more effective than C225 in inhibiting the growth of A431 xenograft tumors. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the chimerized antibody of Goldstein for the treatment of human patients having an EGFR dependent tumor with a combination of radiation and an anti-EGFR antibody as taught by Goldstein. One would have been motivated by the teachings of Saleh that a combination of radiation and anti-EGFR antibody produced a greater effect than either treatment alone. One would have had a reasonable expectation of success because of the teachings of Goldstein that a chimerized version of the C225 antibody appears to have a greater anti-tumor effect than does the parent antibody.

Claims 31-39 include limitations concerning the order in which the antibodies and radiation are administered. The combination of Saleh and Goldstein does not explicitly teach each and every administration schedule of claims 31-39. However, it would be obvious to one of ordinary skill in the art of treating cancer patients how to optimize a treatment schedule. Such optimization of treatment does not appear to add an inventive step to the claimed inventions. See

MPEP 2144.05: A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 24 and 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 11/206,825. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending 11/205,825 anticipate the claims of the instant case. The claims of the copending application are drawn to methods of inhbiting tumor growth comprising administering antibodies hat bind to EGFR, at least one chemotherapeutic agent and radiation therapy. Thus, these claims are a species of the claims of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
June 25, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER